MEYER, 1998

23 December 1998

MEMORANDUM FOR US EPA
NCEA (MD-52)
RTP, NC 27711
ATTN: Annie M. Jarabek

FROM: AFRL/HEST
Operational Toxicology Branch
2856 G St
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SUBJECT: Consultative Letter, AFRL-HE-WP-CL-1998-0035, Pharmacokinetic Data for Iodide Uptake Inhibition in the Thyroid by Perchlorate

1. The Operational Toxicology Branch has performed two pharmacokinetic intravenous dosing studies with adult male Sprague-Dawley rats.

   a. Study_1- Rats were dosed once by intravenous tail vein injection with 33 μg/Kg of non-radiolabeled iodide and ^{125}I mixed in physiologic saline. Rats were killed at selected times (n=6 per time point) up to 24 hours. Total and free ^{125}I were measured in serum, thyroid, and urine. This is called a control study. Another control study is underway.

   b. Study_2- Rats were dosed once by intravenous tail vein injection with either 0.01, 0.1, 1.0 or 3.0 mg/Kg of cold ammonium perchlorate mixed in saline. Perchlorate was administered as ammonium perchlorate dissolved in physiologic saline and was expressed as mg perchlorate/kg body weight. Two hours after dosing with perchlorate the rats were dosed by intravenous tail vein injection with 33μg/Kg ^{125}I dissolved in saline. Rats were killed at selected times (n=6 per time point) up to 24 hours. Total and free ^{125}I were measured in serum, thyroid, and urine. Perchlorate serum, thyroid, tissue and urine analyses will begin in January 1999.

2. Inhibition of ^{125}I uptake into the thyroid was best demonstrated for measurement of bound ^{125}I in the thyroid at 2, 6, and 9 hours after dosing with ^{125}I (Fig. 1). This corresponds to 4,8, and 11 hours, respectively, after dosing with ammonium perchlorate. The most pronounced inhibitory effects were found at the 1 and 3 mg/kg perchlorate dose groups. However, the trend of ^{125}I inhibition is evident at the lower dose groups (0.1 and 0.01 mg/kg). By 24 hours after dosing with ^{125}I (26 hours after dosing with ammonium perchlorate), the inhibitory effects of perchlorate on ^{125}I uptake in the thyroid were still observed in the 1 and 3 mg/kg perchlorate dose groups. Table 1 provides the percent inhibition of ^{125}I uptake as measured by bound ^{125}I in the thyroid for 2, 6, and 9 hours after dosing with ^{125}I (4,6, and 11 hours after dosing with ammonium perchlorate). Perchlorate induced inhibition of uptake of ^{125}I in the thyroid as measured by bound ^{125}I was 82, 55, 29, and 11% at 9 hours after dosing with ^{125}I for the 3, 1, 0.1, 0.01 mg/kg dose groups, respectively.

3. Fig. 2 shows the inhibition of ^{125}I uptake into the thyroid by perchlorate as measured by free ^{125}I in thyroid. Inhibition is best demonstrated at 9 and 24 hours after dosing with ^{125}I for the 0.1, 1 and 3 mg/kg dose groups.

4. The amount of bound ^{125}I in serum was elevated in perchlorate dosed animals compared to controls (^{125}I dosed rats) for up to 6 hours in all dose groups. Elevated bound ^{125}I was observed in serum for up to 9 hours in the 0.01 mg/kg dose group (11 hours after ammonium perchlorate dosing) (Fig. 3). These data suggests that thyroid function was altered by perchlorate and a transient "discharge" of organified ^{125}I occurred. Free ^{125}I levels in serum were similar between perchlorate-dosed rats and control ^{125}I-dosed rats (Fig. 4).

5. Recover of ^{125}I in urine 24 hours after dosing with ^{125}I was between 79 to 88% for control ^{125}I-dosed animals and perchlorate dosed animals. The control ^{125}I –dosed rats excreted 79.5% (SD±5.50) of their ^{125}I dose in urine over a 24-hour period. The 0.01, 0.1, 1.0 and 3.0 mg/kg perchlorate dose groups excreted 87% (±7.84), 86% (±4.47), 87.8 %(±20.20) and 79.3(±10.58), of their ^{125}I dose in urine, respectively, over a 24-hour period.

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Deputy Chief, Operational Toxicology Branch

Attachment
Four Figures and one Table

Inhibition of Iodide Uptake by Perchlorate in the Thyroid Gland

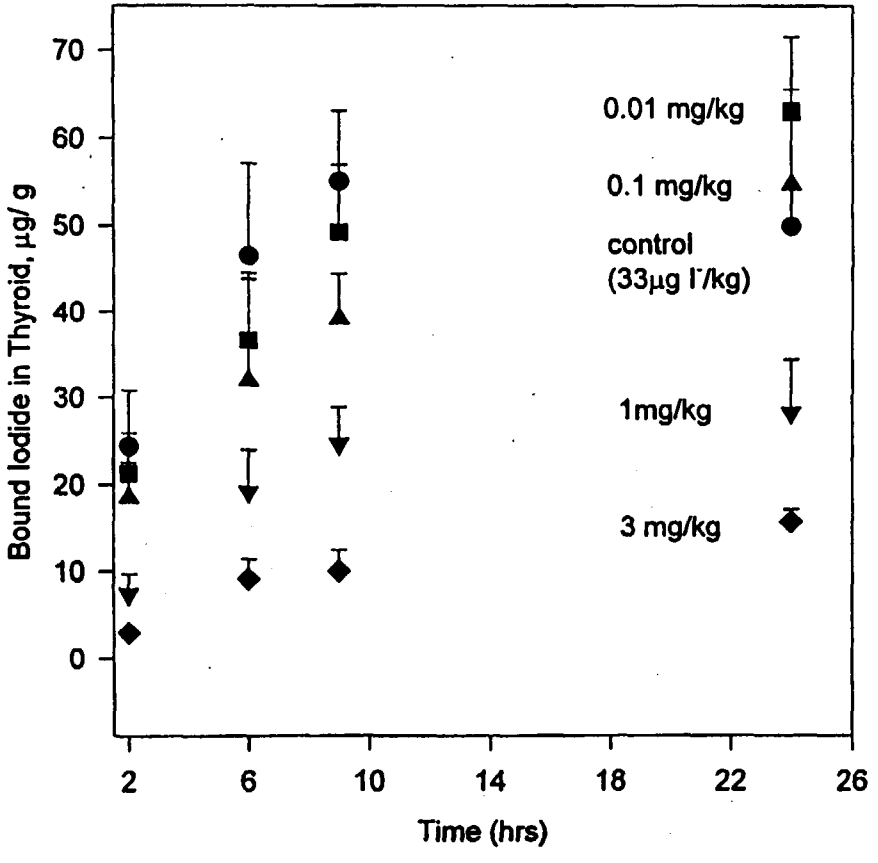

Fig. 1

Inhibition of Ioddie Uptake by Perchlorate in the Thyroid Gland

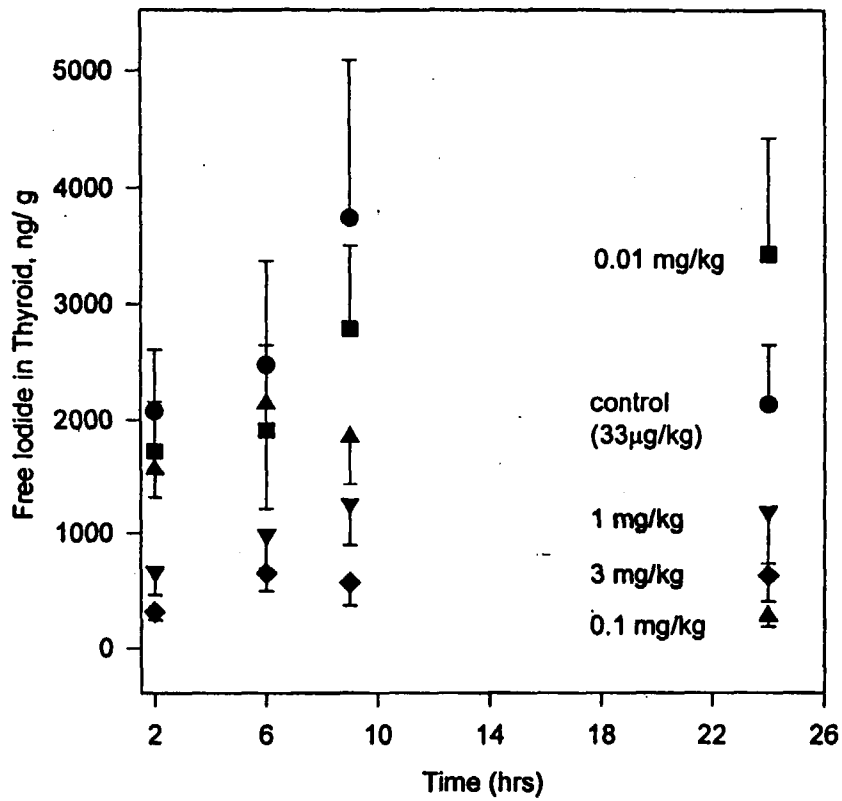

Fig. 2

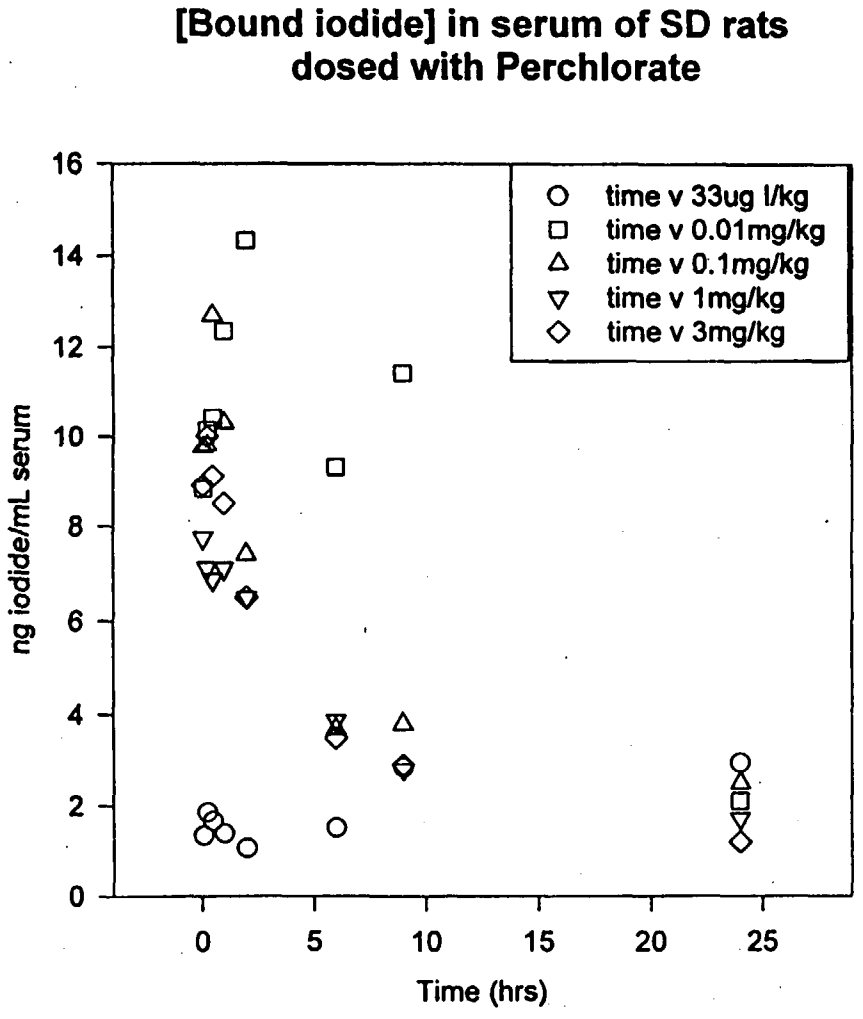
[Bound iodide] in serum of SD rats
dosed with Perchlorate
time v 33ug I/kg
time v 0.01mg/kg
time v 0.1mg/kg
time v 1mg/kg
time v 3mg/kg
ng iodide/mL serum
0
2
4
6
8
10
12
14
16
0
5
10
15
20
25
Time (hrs)

Fig. 3

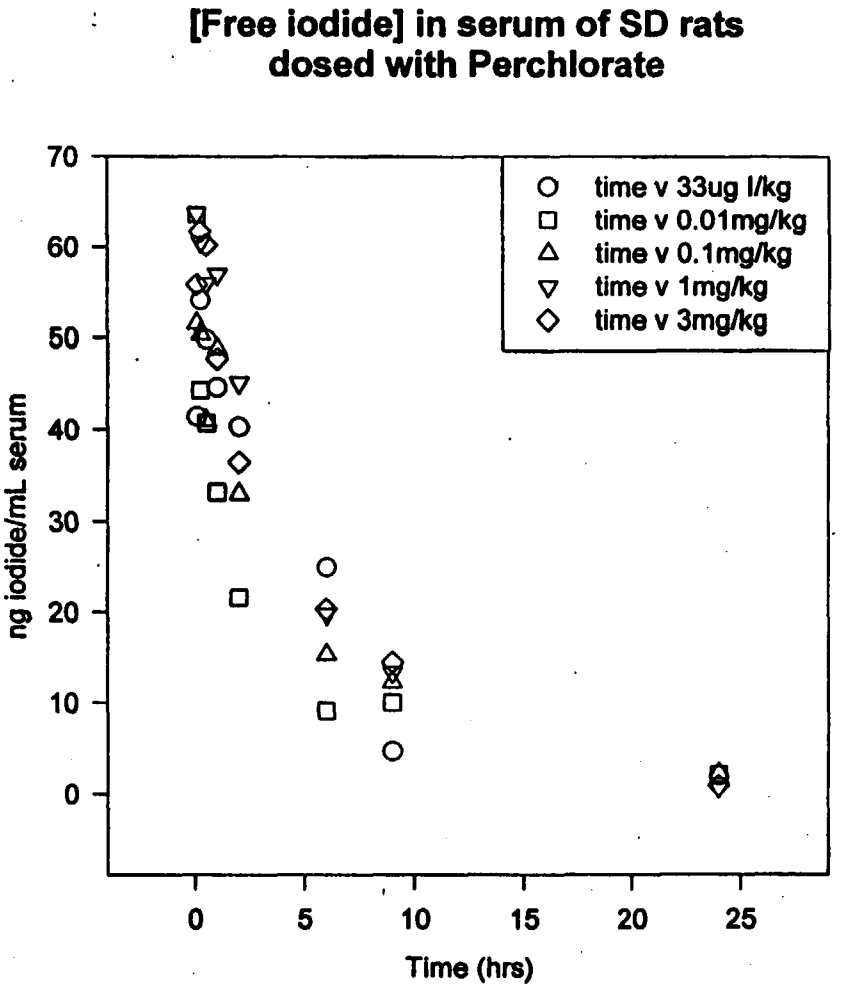
[Free iodide] in serum of SD rats dosed with Perchlorate
ng iodide/mL serum
Time (hrs)
time v 33ug I/kg
time v 0.01mg/kg
time v 0.1mg/kg
time v 1mg/kg
time v 3mg/kg
0
10
20
30
40
50
60
70
0
5
10
15
20
25

Fig. 4

Table 1. Percent inhibition of iodide uptake in the thyroid gland of SD rats dosed with perchlorate.

Time points	Dose mg perchlorate/ kg	[iodide] µg/g	% of inhibition
2 h	Control*	24.4	-
	0.01	21.3	13
	0.1	18.6	24
	1	7.4	70
	3	2.99	88
6 h	Control*	46.5	-
	0.01	36.7	21
	0.1	32	31
	1	19.2	59
	3	9.13	80
9 h	Control*	55	-
	0.01	49.2	11
	0.1	39.2	29
	1	24.7	55
	3	10	82

*dosed with only iodide (33µg/kg).